Different menopausal hormone regimens and risk of breast cancer

Running title: Menopausal hormones and breast cancer

Nele BRUSSELAERS, MD MSc PhD[1,2] Rulla M TAMIMI, MSc ScD[3] Peter KONINGS,[4] Hans- Olov ADAMI, MD PhD[5,6] Jesper LAGERGREN, MD PhD[4,7]

[1]Centre for Translational Microbiome Research, Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Nobelsväg 16, 17177 Stockholm, Sweden.
[2]Science for Life Laboratory, Tomtebodavägen 23a, 171 65 Stockholm, Sweden.
[3]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA, Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, 677 Huntington Avenue. Boston, Massachusetts 02115, USA.
[4]Upper Gastrointestinal Surgery, Department of Molecular Medicine and Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Norra Stationsgatan 67, 17176 Stockholm, Sweden.
[5]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Nobelsväg 12A, Stockholm, Sweden.
[6]Clinical Effectiveness Research Group, Institute of Health and Society, University of Oslo, Kirkeveien 166, 0450 Oslo, Norway.
[7]Division of Cancer Studies, King's College London, London WC2R 2LS, United Kingdom

Positions: NB: associate professor of clinical epidemiology; RT, associate professor of epidemiology; PK, senior statistician; HOA, professor of cancer epidemiology; JL, professor of surgery.

Funding*:* This work was supported by the Swedish Research Council (839-2008-7496), Swedish Cancer Society (CAN 2015/460), SFO Epidemiology Karolinska Institutet (Young Scholar Grant to Nele Brusselaers), Karolinska Institutet Distinguished Professor Award to Professor Hans-Olov Adami (Dnr: 2368/10-221), and to Professor Jesper Lagergren (Dnr: D-02418/2010). These funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Conflicts of interest: none
Correspondence to: Nele Brusselaers, Centre for Translational Microbiome Research, Dept. Microbiology, Tumor and Cell Biology, Nobelsväg 16, 17177 Stockholm, Sweden.
E-mail: nele.brusselaers@ki.se Tel: +46 8 524 853 08

Word count: 2908

Contributor statement: The study has been designed by all authors, NB conducted and is responsible for the data-analysis, while senior statistician PK conducted the matching. NB drafted the manuscript, which is thoroughly revised and approved by all authors.

Abstract (250 words)

Objective: To assess the different treatment options for menopausal hormone therapy (HT) and the risk of breast cancer.

Methods: Prospective Swedish nationwide cohort study including all women who received ≥1 HT prescription during the study period 2005-2012 (290,186 ever-users), group-level matched (1:3) to 870,165 never-users. HT, ascertained from the Prescribed Drug Register, was subdivided by estrogen and progestogen formulation types, regimens (continuous vs. sequential) and modes of administration (oral vs. transdermal). The risk of invasive breast cancer is presented as adjusted odds ratios (ORs) and 95% confidence intervals (CI).

Results*:* Current use of estrogen-only therapy (ET) was associated with a slight excess breast cancer risk (OR=1.08, 95% CI 1.02-1.14). The risk for current estrogen plus progestogen (EPT) therapy was higher (OR=1.77, 95% CI 1.69-1.85) and increased with higher age at initiation; among women 70+ years the OR was 3.59 (95% CI 3.30-3.91). In contrast, past use was associated with reduced breast cancer risk. Current continuous EPT use was associated with higher risk (OR=2.18, 95% CI 1.99-2.40 for progesterone-derived; OR=2.66, 95% CI 2.49-2.84 for testosterone-derived) than sequential use (OR=1.37, 95% CI 0.97-1.92 for progesterone-derived; OR=1.12, 95% CI 0.96-1.30 for testosterone-derived). The OR for current use was 1.12 (95% CI 1.04-1.20) for estradiol, 0.76 (95% CI 0.69-0.84) for estriol, 4.47 (95% CI 2.67-7.48) for conjugated estrogens, and 1.68 (95% CI 1.51-1.87) for tibolone. Oral and cutaneous HT showed similar associations.

Conclusions*:* Different HT regimens have profoundly different effects on breast cancer risk. This knowledge may guide clinical decision-making when HT is considered.

Introduction

Menopausal hormone therapy (HT) alleviates menopause-related symptoms and prevents osteoporotic fractures,[1] but HT has been associated with an increased breast cancer risk.[2] In two large prospective studies, short-term use of estrogen-only therapy (ET) did not increase the risk of breast cancer, yet longer-term use did.[3, 4] Current recommendations state that HT for up to three to five years could be beneficial for women <60 years, while the excess risk of breast cancer in women >70 years is a relative contraindication,[5] and that duration of HT should not exceed 3-5 years.

It is well-established that adding progestogens to HT reduces the excess risk of endometrial cancer,[6] however several studies suggest that estrogen+progestogen (EPT) formulations increase breast cancer risk.[4, 7-11] Data are limited regarding the effects of different types of estrogens and progestogens, formulations, regimens and modes of administration of HT on breast cancer risk.[2] Using cutaneous (patch) estrogens, which avoid the first-pass effect in the liver, may avoid the increased risk observed with oral use, but there is a need for studies examining this potential difference.

After publication of a trial demonstrating an increased risk of breast cancer,[12] use of HT has dropped dramatically over the last 15 years.[13] The aims of this study were to assess the risk of breast cancer following contemporary HT while taking advantage of the wide range of HT regimens used in Sweden and to identify regimens that minimize any excess risk of breast cancer.

Methods

Cohort

Since 1st July 2005, the Swedish Prescribed Drug Registry has recorded individual-level data on all drugs prescribed and dispensed in Sweden with >99% completeness.[14] Drugs dispensed over-the-counter and within hospitals are not included. Each record includes a Swedish personal identity number, individual characteristics, Anatomical Therapeutic and Chemical classification (ATC) codes, modes of administration, dates of prescribing and dispensing, and defined daily dosage (DDD) per package, i.e. “the assumed average maintenance dose per day for a drug used for its main indication in adults” as defined by the World Health Organisation.

All women with at least one dispensed HT prescription between 1st July 2005 and 31st December 2012 were identified.[15] Ever HT-users were matched 1:3 on year of birth to women with no HT prescriptions. Both HT users and non-HT users were excluded if they were younger than 40 years, or if there was a history of malignancy (except non-melanoma skin cancer) identified from the Swedish Cancer Register (see below) at the time of their first HT prescription (users) or start of the study period (non-HT users). The group-level matching reduced model dependence and facilitated unbiased assessment of multiple outcomes.[16] Women were first stratified on three binary variables which might influence prescription of HT: parity (parous/nulliparous), history of thrombotic events, and hysterectomy. Within each of these eight strata, ever HT users were matched to the “nearest neighbor” never HT user on year of birth, diabetes, obesity, smoking-related disorders, and alcohol-related disorders.

Information on these variables was obtained from the discharge diagnoses in the Swedish Patient Registry (described below).

Classification of menopausal hormone therapy

The following HT formulation types (with ATC codes) were considered: estrogens (G03C), progestogens (G03D and G03C), and estrogens and progestogens (G03F, categorized as G03FA for fixed combinations and G03FB for sequential preparations). If persons were prescribed 1 progestogen HT during the study period, they were considered EPT users, otherwise ET users. Progestogens were subdivided into progesterone-derived (medroxyprogesterone) and testosterone-derived formulations (norethisterone, levonorgestrel, lynestrenol and dienogest).[17] Estrogens were categorized as estradiol (G03CA01 and G03CA03), estriol (G03CA04), conjugated-estrogens (G03CA57), and tibolone (G03CX01). Persons switching HT types during the study period were excluded from the sub-analyses. For G03F EPT combinations, estradiol accounted for >99% of all prescriptions. We considered only systemic HT administration, i.e. oral or cutaneous excluding vaginal, which is not available over-the-counter in Sweden. Injectable HT is not used in Sweden.

The duration of HT was estimated based on the DDD per package, taking potency of the drug and prescribed quantities into account as defined by the World Health Organization. The maximum allowed time covered by a prescription dispensation in Sweden is 3 months.[14] Therefore, allowing for a wash-out period, current users were those with at least 1 dispensed prescription of HT during the last six months (180 days) of follow-up. All the others were considered past-users. Because the

Prescribed Drug Registry began July 1, 2005, HT prescriptions before that date were not available.

The majority of the ever-users had at least one prescription in 2005 (N=173,465; 59.8%) and had an unknown starting date of HT. An additional 12.1% women (N=35,090) prescribed HT entered in 2006, 6.8% in 2007 (N=19,640), 5.1% in 2008 (N=14,860), and approximately 4% each year thereafter. To reduce misclassification (underestimation) of HT duration, the analyses based on person time focused on those with a first recorded prescription in 2006 onwards. A sensitivity analysis included only women without HT prescriptions in 2005 and 2006 and their first prescription in 2007 or later.

Follow-up

The personal identity number allowed linkage to the nationwide Swedish registries of cancer, patient data, and causes of death. The Swedish Cancer Registry, founded in 1958 and more than 98% complete,[18] was used to identify all incident invasive breast cancers. Estrogen receptor information is not available from the Registry. In the Swedish Patient Registry, with nationwide coverage of all in-hospitalizations since 1987 and specialist out-patient care visits since 2001, diagnoses and surgical procedures are recorded. This registry was used to ascertain ever parous (based on record of delivery), hysterectomy, and co-morbidities that might confound the association between HT and breast cancer (e.g., osteoporosis, smoking-related diseases, alcohol related diseases, thrombotic events, obesity, and diabetes mellitus). The Swedish Causes of Death Registry, which was established in 1952 and is 100% complete, was used to collect date of death. The study was approved by

Regional Ethical Review Board in Stockholm (2014/1291-31/4), and the need for informed consent was not required.

Statistical analysis

Conditional logistic regression, taking into account clustering by the exact-matching variables, was used for analyses evaluating ever use versus never use. Multivariable models were also adjusted for all 8 matching variables as well as osteoporosis, providing adjusted odds ratios (OR) and 95% confidence intervals (CIs). These analyses compared HT ever-users, current-users and past-users with never-users for the whole study period (2005-2012).

To assess the relation between duration of HT and breast cancer risk, multivariable Cox regression models provided hazard ratios (HRs) and 95% CIs. Multivariable models were adjusted for the matching variables (using age at first prescription instead of year of birth), osteoporosis, duration of treatment, and formulations and regimens of HT if appropriate. Duration of HT (estimated by the total sum of DDD per package), was categorized as <12 month, 12-35 months, ≥36 months, using the <12 months as reference group. Because the Prescribed Drug Registry began in July 2005, we excluded individuals enrolled in 2005 (with uncertain start date of exposure) and cancers occurring within 12 months of enrolment for all Poisson models. Time of follow-up was calculated from the date of the first prescription, to the first cancer (breast or other types of cancer, i.e. competing risk), death, or end of the study period (December 31, 2012), whichever occurred first. All analyses were performed with Stata MP14 (Stata Corp).

Results

Descriptive characteristics

The cohort included 290,186 ever-users of HT and 870,165 matched never-users. Age and other characteristics were equally distributed among HT users and never-users (Table 1). ET was almost as common (46.9%, N=135,988) as EPT combination HT (53.1%, N=154,198). The primary mode of administration was oral (84.0%, N=243,682), while 12.3% (N=35,826) used cutaneous HT and 3.7% used both (N=10,678). Among ET users, the most common formulations of estrogen were estradiol (39.2%, N=53,339) and estriol (40.9%, N=55,653), followed by tibolone (13.2%, N=17,992) and conjugated-estrogens (0.9%, N=1,161).

Among women using EPT, continuous EPT was more common (60.0%, N=92,381) than sequential combinations (18.3%, N=28,263). Additionally, testosterone-derived progestogens were administered more frequently (55.6%, N=85,659) than progestogen-derived progestogens (30.7%, N=47,308). The most commonly used EPT was testosterone-derived progestogens administered continuously (34.6%, N=53,360).

Menopausal hormone therapy and overall risk of breast cancer

Compared to never-users of HT, ever-users did not have an increased risk of breast cancer (OR=1.02; 95% CI 0.99-1.05) (Table 2). However, there were important differences in risk of breast cancer by type of formulation, age at initiation, as well as current versus past use. Compared to never-users, current users had an increased risk of breast cancer (OR=1.38, 95% CI 1.33-1.43), and the association was stronger for EPT users (OR=1.77, 95% CI 1.69-1.85) than ET users (OR=1.08, 95% CI 1.02-

1.14). Among current users of EPT, there was increasing risk of breast cancer with later age of initiation, and among women who began HT use at age 70 or later, current users of EPT had a more than threefold increased risk of breast cancer compared with never-users (OR=3.59, 95% CI 3.30-3.91). In contrast, past users of HT were at a decreased risk of breast cancer compared with never-users (OR=0.75, 95% CI 0.72-0.79). This inverse association was stronger for past use of estrogen only HT (OR=0.63, 95% CI 0.60-0.67) than for EPT (OR=0.89, 95% CI 0.84-0.93).

Duration of menopausal hormone therapy and risk of breast cancer

The analyses of duration of HT were restricted to women with a first recorded prescription in 2006 (Table 3). Comparing ever-users exposed ≥12 months to those exposed <12 months, showed no increased risk of breast cancer (HR=1.03, 95% CI 0.91-1.16). However, when examining specific HT types, the risk of breast cancer was increased among women using EPT ≥12 months (HR=1.17, 95% CI 1.00-1.38), but not for ET users (HR=0.89, 95% CI 0.74-1.07). Among current-users, the excess risk of breast cancer was highest among women younger than 60, especially among those using EPT for 12-35 months (HR=1.68, 95% CI 1.04-2.72).

Estrogen-formulations of menopausal hormone therapy and risk of breast cancer

Among estrogen only HT-users, different estrogen formulations were differentially associated with risk of breast cancer (Table 4). Ever-users of ET had an overall decreased risk of breast cancer compared to never-users (OR=0.83, 95% CI 0.80-0.87), while current-users had a modestly increased risk (OR=1.08, 95% CI 1.02-1.14). However, specific formulations of estrogens were associated with an increased risk of breast cancer. Ever-users of conjugated estrogens had a 33% increased risk (OR=1.33, 95% CI 1.00-1.77) and ever-users of tibolone had a 15% (OR=1.15, 95%

CI 1.06-1.25) increased risk of breast cancer compared to never-users. The association was stronger among current-users of conjugated-estrogens (OR=4.47, 95% CI 2.67-7.48) and tibolone (OR=1.68, 95% CI 1.51-1.87) although based on much smaller groups.

Progestogen-formulations of menopausal hormone therapy and risk of breast cancer

The risk of breast cancer for different formulations and usage-patterns of progestogens for women using combined EPT therapy is presented in Table 4. Compared to the never-users, risk of breast cancer was increased following ever continuous (daily) use of progestogens (OR=1.24, 95% CI 1.20-1.28). The risk was increased among users of continuous combinations of testosterone-derived progestogens (OR=1.63, 95% CI 1.55-1.71), but also progesterone-derived progestogens (OR=1.38, 95% CI 1.28- 1.48). In contrast, the sequential combinations of progestogens in ever-users were associated with either no increased risk or a reduced risk (Table 4). Among current-users, the magnitude of risks were higher among all progestogen-users, in particular for testosterone-derived continuous combinations (OR=2.66, 95% CI 2.49-2.84) and progesterone-derived continuous combinations (OR=2.18, 95% CI 1.99-2.40).

Mode of menopausal hormone therapy administration and risk of breast cancer

The associations between oral versus cutaneous HT and breast cancer are presented in Table 5. Descriptive frequencies of the types of oral and cutaneous hormone therapy are included in E3. Compared to never-users, the risk of breast cancer was highest among ever-users of oral HT (OR=1.44, 95% CI 1.39-1.50), especially among current-users of oral EPT (OR=1.86, 95% CI 1.77-1.95) (Table 5).

Current cutaneous use of ET (OR=1.19, 95% CI 1.05-1.36) and EPT (OR=1.40, 95% CI 1.20-1.64) was also associated with an increased risk of breast cancer. Although there was heterogeneity in formulations of cutaneous regimens, the statistical power was insufficient to evaluate individual formulations.

Discussion

This study evaluating the association of contemporary menopausal hormone therapies with breast cancer risk showed that different HT regimens have different effects on breast cancer risk. As previous studies of older generations of HT have reported,[4, 7, 19-21] this study found that current use of EPT was associated with an increased risk of breast cancer. Estrogen only HT was also associated with an increased risk, but the magnitude of association was much more modest.

This study has a number of strengths, including the large sample size, population-based study design, and contemporary formulations of HT. In addition, the Swedish Prescribed Drug Registry allowed for high quality and detailed information on HT formulations and nationwide coverage. The unique matched cohort design allowed for HT-users and non-users to be balanced on several potential confounders. This group-level matching enabled us to create two groups with a similar probability of being treated with HT, a similar approach as used in propensity-scoring matching, therefore limiting the risk of selection bias and confounding. This method also takes into account the problem with exposure time for never-users (who do not have a start date of exposure); yet the relative effect of duration of use was evaluated among different groups of HT users.

This study also has some limitations. The main limitation is that the Swedish Prescribed Registry did not begin until 2005. This resulted in incomplete information on first date of prescription and as a result also incomplete data on duration of use. In secondary analyses, we restricted analyses to new prescriptions during the study period. In general, although the number of cases of breast cancer dropped, we found results that were very consistent with the main analysis. Additionally, we were limited in our ability to assess longer durations of use. Although older studies have demonstrated that longer duration of HT increases the risk of breast cancer, we could not assess this in the present cohort.

We were also limited by availability of data coming from Swedish registries. We used the Patient Registry to control for potential confounders; however, we were unable to adjust for a number of known breast cancer risk factors such as reproductive factors and body mass index. Additionally, information on some factors such as hysterectomy and parity may be under ascertained for those occurring prior to the start of the registry, or may only reflect more severe cases (e.g. obesity). However, previous studies, which present both adjusted and unadjusted estimates suggest that confounding by established breast cancer risk factors is minimal.[11] Additionally, we were unable to evaluate interactions between HT and factors such as body mass index and age at menopause, which others have reported with standard hormone therapy doses.[4, 10] We were also unable to assess the association by family history, benign breast disease or tumor estrogen receptor (ER) status, since the Cancer Registry did not contain this information. A national mammography screening program has been established in 1994 in Sweden, inviting all women aged 40-74 years every 18-24 months.[22-24] Although approximately 80% attend the screening,[23]

women on HT may be more likely to attend but no information on screening attendance was available. Unfortunately we did not have information on the starting age of menopause[25], in particular for the non-users. Among our HT users, 14.4% was younger than 50 at the time of their first prescription. Although we used age 40 to avoid premature menopause, some non-users may not have started menopause yet giving them a higher probability of breast cancer compared to menopausal women of the same age.[26] This may explain some of the apparent protective effects of HT in the younger age group. When those younger than 50 at the start of the study period were excluded, the risk of breast cancer among the youngest group of current users was OR=1.10 (95% CI 1.05-1.15) compared to OR=1.02 (95% CI 0.99-1.05) in the whole youngest age-group.

Since the publication of WHI results in 2002, demonstrating an increased risk of breast cancer with EPT, prescription patterns for estrogen plus progestogen therapies have declined,[27] and formulations and patterns of use have changed.[28] The standard dose of estrogens in oral HT used in the WHI trial and prior to 2001 included 0.625mg conjugated equine estrogens. Guidelines now recommend low-dose and short-term use of oral HT.[29, 30] Additionally, transdermal HT have also been advocated.[31, 32] In line with these recommendations, the prevalence of women prescribed standard dose oral HT has declined in the US and Europe, while use of low-dose oral formulations as well as transdermal preparations have increased.[33-37] One of the main contributions of the current study is the ability to examine different types of estrogens and progestogens, formulations, regimens, and modes of administration. Combined EPT regimens with continuous progestogens were associated with a more than threefold increased risk compared to never users. In

contrast, the sequential formulations were only suggestively associated with risk. These results have important public health implications. They suggest that for women interested in taking HT, sequential formulations are less associated with breast cancer risk compared to other EPT.

We also found that current cutaneous use of EPT was associated with an increased risk of breast cancer. Although cutaneous use of EPT had a slightly lower risk than was observed with oral HT, this study provided much needed information on the risks associated with cutaneous HT. These findings argue against the hypothesis that cutaneous HT may not be associated with breast cancer to the same extent as oral HT since it avoids the first-pass effect in the liver (cutaneous estrogen may not increase sex hormone-binding globulin to the extent that oral preparations do).[38] We also observed an inverse association with past use of HT, which is consistent with some prior studies,[2, 11] but not all.[20] It has been hypothesized that past-users are more likely to have shorter durations of use than current-users, and that these women may be using HT for the short-term relief of menopausal symptoms. Moreover, women who initiate HT tend to be leaner and may be at a reduced risk of developing breast cancer.[39-41]

Conclusions

In conclusion, this large population-based study found that risk of breast cancer differed substantially by various contemporary formulations of HT. These data fill important gaps in our knowledge and may help clinical decision-making when considering the benefits and potential harms of HT for relief of menopausal symptoms.

Acknowledgements: We are grateful to all thousands of patients, physicians and healthcare staff members who contributed to the data collection, and to the Swedish National Board of Health and Welfare that collected the data. NB had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. North American Menopause Society. Estrogen and progestogen use in postmenopausal women: 2010 position statement of The North American Menopause Society. *Menopause* 2010; **17**: 242-55.

2. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet* 1997; **350**(9084): 1047-59.

3. Chen WY, Manson JE, Hankinson SE, et al. Unopposed estrogen therapy and the risk of invasive breast cancer. *Arch Intern Med* 2006; **166**(9): 1027-32.

4. Beral V, Million Women Study C. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003; **362**(9382): 419-27.

5. Rozenberg S, Vandromme J, Antoine C. Postmenopausal hormone therapy: risks and benefits. *Nat Rev Endocrinol* 2013; **9**(4): 216-27.

6. Weiderpass E, Adami HO, Baron JA, et al. Risk of endometrial cancer following estrogen replacement with and without progestins. *J Natl Cancer Inst* 1999; **91**(13): 1131-7.

7. Bergkvist L, Adami HO, Persson I, Hoover R, Schairer C. The risk of breast cancer after estrogen and estrogen-progestin replacement. *N Engl J Med* 1989; **321**(5): 293-7.

8. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. *Am J Epidemiol* 2000; **152**(10): 950-64.

9. Bakken K, Fournier A, Lund E, et al. Menopausal hormone therapy and breast cancer risk: impact of different treatments. The European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2011; **128**(1): 144-56.

10. Magnusson C, Baron JA, Correia N, Bergstrom R, Adami HO, Persson I. Breast-cancer risk following long-term oestrogen- and oestrogen-progestin-replacement therapy. *Int J Cancer* 1999; **81**(3): 339-44.

11. Tamimi RM, Hankinson SE, Chen WY, Rosner B, Colditz GA. Combined estrogen and testosterone use and risk of breast cancer in postmenopausal women. *Arch Intern Med* 2006; **166**(14): 1483-9.

12. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *Jama* 2002; **288**(3): 321-33.

13. Manson JE, Kaunitz AM. Menopause Management--Getting Clinical Care Back on Track. *N Engl J Med* 2016; **374**(9): 803-6.

14. Jarvstrat L, Spetz Holm AC, Lindh-Astrand L, Hoffmann MJ, Fredrikson MG, Hammar ML. Use of hormone therapy in Swedish women aged 80 years or older. *Menopause* 2015; **22**(3): 275-8.

15. Brusselaers N, Maret-Ouda J, Konings P, El-Serag HB, Lagergren J. Menopausal hormone therapy and the risk of esophageal and gastric cancer. *Int J Cancer* 2016.

16. National Collaborating Centre for Women's Children's Health. National Institute for Health and Care Excellence: Clinical Guidelines. Menopause: Full Guideline. London: National Institute for Health and Care Excellence (UK) Copyright (c) 2015 National Collaborating Centre for Women's and Children's Health.; 2015.

17. Schindler AE, Campagnoli C, Druckmann R, et al. Classification and pharmacology of progestins. *Maturitas* 2008; **61**(1-2): 171-80.

18. Barlow L, Westergren K, Holmberg L, Talback M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. *Acta oncologica* 2009; **48**(1): 27-33.

19. Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N Engl J Med* 1995; **332**(24): 1589-93.

20. Fournier A, Mesrine S, Dossus L, Boutron-Ruault MC, Clavel-Chapelon F, Chabbert-Buffet N. Risk of breast cancer after stopping menopausal hormone therapy in the E3N cohort. *Breast cancer research and treatment* 2014; **145**(2): 535-43.

21. Antoine C, Ameye L, Paesmans M, de Azambuja E, Rozenberg S. Menopausal hormone therapy use in relation to breast cancer incidence in 11 European countries. *Maturitas* 2016; **84**: 81-8.

22. Reduction in breast cancer mortality from organized service screening with mammography: 1. Further confirmation with extended data. *Cancer Epidemiol Biomarkers Prev* 2006; **15**(1): 45-51.

23. Gabrielson M, Eriksson M, Hammarstrom M, et al. Cohort profile: The Karolinska Mammography Project for Risk Prediction of Breast Cancer (KARMA). *Int J Epidemiol* 2017.

24. Olsson S, Andersson I, Karlberg I, Bjurstam N, Frodis E, Hakansson S. Implementation of service screening with mammography in Sweden: from pilot study to nationwide programme. *J Med Screen* 2000; **7**(1): 14-8.

25. Morabia A, Costanza MC. International variability in ages at menarche, first livebirth, and menopause. World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives. *Am J Epidemiol* 1998; **148**(12): 1195-205.

26. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet* 1997; **350**(9084): 1047-59.

27. Majumdar SR, Almasi EA, Stafford RS. Promotion and prescribing of hormone therapy after report of harm by the Women's Health Initiative. *Jama* 2004; **292**(16): 1983-8.

28. Fournier A, Weiderpass E. Characteristics and recent evolution of menopausal hormone therapy use in a cohort of Swedish women. *Climacteric* 2009; **12**(5): 410-8.

29. ACOG Committee Opinion No. 420, November 2008: hormone therapy and heart disease. *Obstetrics and gynecology* 2008; **112**(5): 1189-92.

30. ACOG Practice Bulletin No. 141: management of menopausal symptoms. *Obstet Gynecol* 2014; **123**(1): 202-16.

31. Buster JE. Transdermal menopausal hormone therapy: delivery through skin changes the rules. *Expert Opin Pharmacother* 2010; **11**(9): 1489-99.

32. Canonico M, Plu-Bureau G, Lowe GD, Scarabin PY. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *BMJ* 2008; **336**(7655): 1227-31.

33. Steinkellner AR, Denison SE, Eldridge SL, Lenzi LL, Chen W, Bowlin SJ. A decade of postmenopausal hormone therapy prescribing in the United States: long-term effects of the Women's Health Initiative. *Menopause* 2012; **19**(6): 616-21.

34. Ettinger B, Wang SM, Leslie RS, et al. Evolution of postmenopausal hormone therapy between 2002 and 2009. *Menopause* 2012; **19**(6): 610-5.

35. Fournier A, Kernaleguen C, Panjo H, Clavel-Chapelon F, Ringa V. Postmenopausal hormone therapy initiation before and after the Women's Health Initiative in two French cohorts. *Menopause* 2011; **18**(2): 219-23.

36. Du Y, Scheidt-Nave C, Schaffrath Rosario A, Ellert U, Doren M, Knopf H. Changes of menopausal hormone therapy use pattern since 2000: results of the Berlin Spandau Longitudinal Health Study. *Climacteric* 2009; **12**(4): 329-40.

37. Skouby SO, Barlow D, Samsioe G, et al. Climacteric medicine: European Menopause and Andropause Society (EMAS) statements on postmenopausal hormonal therapy. *Maturitas* 2004; **48**(1): 19-25.

38. Goodman MP. Are all estrogens created equal? A review of oral vs. transdermal therapy. *Journal of women's health* 2012; **21**(2): 161-9.

39. Parazzini F. Trends of determinants of hormone therapy use in Italian women attending menopause clinics, 1997-2003. *Menopause* 2008; **15**(1): 164-70.

40. Oddens BJ, Boulet MJ. Hormone replacement therapy among Danish women aged 45-65 years: prevalence, determinants, and compliance. *Obstetrics and gynecology* 1997; **90**(2): 269-77.

41. Progetto Menopausa Italia Study Group. General and medical factors associated with hormone replacement therapy among women attending menopause clinics in Italy. *Menopause* 2001; **8**(4): 290-5.

Table 1. Characteristics of all women (≥40 years) prescribed systemic menopausal hormone therapy (MHT) in Sweden between July 2005 and December 2012.

	Ever users of MHT	Ever users of estrogen MHT	Ever users of estrogen plus progestin MHT
	Numbers (%)	**Numbers (%)**	**Numbers (%)**
Total	290,186 (100.0)	135,988 (46.9)	154,198 (53.1)
Age at first prescription			
40-49 years	46,299 (16.0)	14,196 (10.4)	32,103 (20.8)
50-59 years	127,773 (44.0)	43,385 (31.9)	84,388 (54.7)
60-69 years	59,592 (20.5)	28,887 (21.2)	30,705 (19.9)
≥70 years	56,522 (19.5)	49,520 (36.4)	7,002 (4.5)
Year of first prescription			
2005-2006	208,555 (71.9)	100,090 (73.6)	108,465 (70.3)
2007-2009	46,736 (16.1)	20,553 (15.1)	26,183 (17.0)
2010-2012	34,895 (12.0)	15,345 (11.3)	19,550 (12.7)

Table 2. The overall risk of cancer following systemic menopausal hormone therapy (MHT) use by MHT regimen and age at first prescription, expressed as standardized incidence ratios (SIR) and 95% confidence intervals (CI).

	Number of observed cases among exposed (%)	SIR (95% CI) All women	<60 years	60-69 years	≥70 years	p for trend	p for effect modification	Absolute Excess number of cases/100,000 person-years
ALL INCIDENT CANCERS								
All MHT	16,813 (5.8)	1.09 (1.07-1.11)	1.08 (1.05-1.12)	1.09 (1.06-1.11)	1.10 (1.07-1.13)	0.00	0.00	212
Estrogen only MHT	8,131 (6.0)	1.04 (1.01-1.06)	1.07 (1.01-1.13)	1.04 (1.00-1.08)	1.02 (0.99-1.06)	0.00		
Estrogen plus progestin MHT	8,682 (5.6)	1.14 (1.12-1.17)	1.09 (1.05-1.13)	1.04 (1.01-1.08)	1.33 (1.26-1.40)	0.00		
MAIN FEMALE REPRODUCTIVE ORGAN CANCERS *(Breast, endometrium, ovaries)*								
All MHT	8,160 (2.8)	1.31 (1.28-1.34)	1.00 (0.96-1.04)	1.48 (1.43-1.53)	1.57 (1.50-1.64)	0.00	0.00	159
Estrogen only MHT	3,452 (2.5)	1.20 (1.16-1.24)	0.93 (0.86-1.00)	1.23 (1.16-1.31)	1.35 (1.28-1.43)	0.00		
Estrogen plus progestin MHT	4,708 (3.1)	1.41 (1.37-1.45)	1.03 (0.98-1.09)	1.65 (1.58-1.73)	2.25 (2.08-2.42)	0.00		
ALL GI TRACT CANCERS *(Esophagus+cardia, liver, gall and bile ducts, pancreas, gut, colon and rectum)*								
All MHT	2,436 (0.8)	0.90 (0.86-0.94)	0.97 (0.89-1.07)	0.90 (0.84-0.96)	0.87 (0.82-0.92)	0.00	0.00	-2
Estrogen only MHT	1,399 (1.0)	0.91 (0.86-0.96)	1.02 (0.86-1.20)	0.95 (0.86-1.05)	0.88 (0.82-0.94)	0.00		
Estrogen plus progestin MHT	1,037 (0.7)	0.88 (0.83-0.94)	0.93 (0.85-1.06)	0.86 (0.78-0.94)	0.84 (0.73-0.95)	0.00		

Table 3. The risk of breast and the main gynecological cancers following systemic menopausal hormone therapy (MHT) use by MHT regimen and age at first prescription, expressed standardized incidence ratios (SIR) and 95% confidence intervals (CI).

	Number of observed Cases (%)	SIR (95% CI) All women	<60 years	60-69 years	≥70 years	p for trend	p for effect modification
BREAST CANCER							
All MHT	6,376 (2.2)	1.24 (1.21-1.27)	1.13 (1.08-1.18)	1.32 (1.27-1.37)	1.28 (1.21-1.35)	0.00	0.00
Estrogen only	2,548 (1.9)	1.05 (1.01-1.10)	1.09 (1.00-1.18)	1.09 (1.02-1.16)	1.00 (0.93-1.07)	0.14	
Estrogen plus progestin	3,828 (2.5)	1.40 (1.36-1.45)	1.15 (1.09-1.21)	1.48 (1.41-1.55)	2.19 (2.01-2.37)	0.00	
ENDOMETRIAL CANCER							
All MHT	1,211 (0.4)	1.12 (1.06-1.19)	0.79 (0.68-0.91)	0.83 (0.75-0.92)	1.75 (1.61-1.90)	0.00	0.71
Estrogen only	646 (0.5)	1.17 (1.08-1.27)	0.44 (0.30-0.62)	0.68 (0.57-0.82)	1.75 (1.59-1.92)	0.00	
Estrogen plus progestin	565 (0.4)	1.07 (0.98-1.17)	0.94 (0.80-1.11)	0.94 (0.82-1.07)	1.78 (1.49-2.11)	0.00	
OVARIAN CANCER							
All MHT	573 (0.2)	1.09 (1.00-1.19)	1.13 (0.97-1.31)	0.99 (0.86-1.14)	1.22 (1.03-1.42)	0.00	0.18
Estrogen only	258 (0.2)	1.03 (0.91-1.17)	1.02 (0.76-1.35)	0.87 (0.69-1.09)	1.18 (0.97-1.41)	0.00	
Estrogen plus progestin	315 (0.2)	1.15 (1.03-1.29)	1.18 (0.98-1.41)	1.08 (0.90-1.28)	1.36 (0.97-1.85)	0.00	

Table 4. The risk of cancers of the gastrointestinal tract following systemic menopausal hormone therapy (MHT) use by MHT regimen and age at first prescription, expressed as standardized incidence ratios (SIR) and 95% confidence intervals (CI).

	Number of observed cases (%)	SIR (95% CI) All women	<60 years	60-69 years	≥70 years	p for trend	p for effect modification
ESOPHAGEAL CANCER (+CARDIA)							
All MHT	86 (0.0)	0.81 (0.64-1.00)	0.53 (0.25-0.97)	0.75 (0.51-1.08)	0.99 (0.71-1.34)	0.00	0.47
Estrogen only MHT	50 (0.0)	0.88 (0.65-1.16)	0.34 (0.04-1.21)	0.83 (0.46-1.40)	1.00 (0.68-1.41)	0.00	
Estrogen plus progestin MHT	36 (0.0)	0.72 (0.50-1.02)	0.62 (0.27-1.21)	0.69 (0.40-1.13)	0.94 (0.43-1.79)	0.03	
GASTRIC CANCER (-CARDIA)							
All MHT	149 (0.1)	0.89 (0.75-1.05)	1.21 (0.85-1.67)	0.81 (0.58-1.10)	0.82 (0.63-1.04)	0.00	0.07
Estrogen only MHT	83 (0.1)	0.84 (0.66-1.05)	0.73 (0.29-1.51)	0.67 (0.36-1.12)	0.91 (0.69-1.19)	0.00	
Estrogen plus progestin MHT	66 (0.0)	0.96 (0.74-1.22)	1.42 (0.97-2.05)	0.91 (0.59-1.33)	0.50 (0.23-0.94)	0.01	
PANCREAS CANCER							
All MHT	311 (0.1)	0.94 (0.84-1.05)	1.03 (0.78-1.33)	0.87 (0.72-1.04)	0.98 (0.81-1.18)	0.00	0.00
Estrogen only MHT	177 (0.1)	0.99 (0.84-1.15)	1.43 (0.93-2.12)	0.98 (0.74-1.27)	0.91 (0.72-1.21)	0.00	
Estrogen plus progestin MHT	134 (0.1)	0.89 (0.74-1.05)	0.84 (0.57-1.18)	0.78 (0.60-1.00)	1.24 (0.86-1.72)	0.00	
GALLBLADDER AND BILE DUCT CANCER							
All MHT	129 (0.0)	0.88 (0.73-1.05)	1.23 (0.81-1.77)	0.72 (0.50-0.99)	0.89 (0.67-1.15)	0.00	0.62
Estrogen only MHT	77 (0.1)	0.91 (0.71-1.15)	1.25 (0.60-2.37)	0.75 (0.43-1.22)	0.93 (0.68-1.24)	0.00	
Estrogen plus progestin MHT	52 (0.0)	0.85 (0.63-1.11)	1.22 (0.73-1.90)	0.69 (0.42-1.06)	0.76 (0.38-1.36)	0.00	
LIVER CANCER							
All MTH	94 (0.0)	0.81 (0.65-0.99)	1.12 (0.72-1.65)	0.81 (0.56-1.11)	0.67 (0.45-0.95)	0.00	0.25
Estrogen only MHT	49 (0.0)	0.77 (0.56-1.02)	1.29 (0.59-2.45)	0.80 (0.45-1.32)	0.65 (0.41-0.97)	0.01	
Estrogen plus progestin MHT	45 (0.0)	0.86 (0.63-1.16)	1.04 (0.59-1.67)	0.81 (0.50-1.24)	0.74 (0.32-1.46)	0.00	
COLON CANCER							
All MHT	1,106 (0.38)	0.90 (0.84-0.95)	0.90 (0.77-1.05)	0.94 (0.85-1.04)	0.87 (0.80-0.95)	0.00	0.00
Estrogen only MHT	660 (0.5)	0.91 (0.84-0.99)	0.91 (0.68-1.19)	0.97 (0.83-1.14)	0.89 (0.80-0.98)	0.00	
Estrogen plus progestin MHT	446 (0.3)	0.88 (0.80-0.97)	0.90 (0.74-1.08)	0.92 (0.0-1.05)	0.80 (0.66-0.97)	0.00	
RECTAL CANCER							
All MHT	561 (0.2)	0.92 (0.84-1.00)	0.99 (0.83-1.17)	0.96 (0.83-1.10)	0.84 (0.72-0.97)	0.0000	0.00
Estrogen only MHT	303 (0.2	0.99 (0.83-1.05)	1.08 (0.79-1.43)	1.06 (0.86-1.30)	0.83 (0.70-0.98)	0.0000	
Estrogen plus progestin MHT	258 (0.2)	0.90 (0.79-1.02)	0.96 (0.77-1.17)	0.88 (0.72-1.06)	0.85 (0.62-1.15)	0.0000	

Table 5. The risk of other cancers following systemic menopausal hormone therapy (MHT) use by MHT regimen and age at first prescription, expressed as standardized incidence ratios (SIR) and 95% confidence intervals (CI).

	Number of observed cases (%)	SIR (95% CI) All women	<60 years	60-69 years	≥70 years	p for trend	p for effect modification
LUNG CANCER							
All MHT	1,333 (0.5)	1.07 (1.02-1.14)	1.25 (1.11-1.39)	1.05 (0.97-1.14)	0.99 (0.90-1.10)	0.00	0.00
Estrogen only MHT	644 (0.5)	1.01 (0.93-1.10)	1.31 (1.07-1.59)	1.16 (1.03-1.31)	0.81 (0.71-0.92)	0.00	
Estrogen plus progestin MHT	689 (0.4)	1.14 (1.05-1.23)	1.22 (1.05-1.40)	0.97 (0.87-1.09)	1.60 (1.35-1.89)	0.00	
MALIGNANT MELANOM							
All MHT	898 (0.3)	1.19 (1.11-1.27)	1.14 (1.01-1.27)	1.30 (1.16-1.44)	1.12 (0.98-1.28)	0.00	0.41
Estrogen only MHT	454 (0.3)	1.26 (1.15-1.39)	1.13 (0.91-1.38)	1.40 (1.19-1.64)	1.23 (1.06-1.42)	0.00	
Estrogen plus progestin MHT	444 (0.3)	1.13 (1.02-1.24)	1.14 (0.99-1.31)	1.22 (1.05-1.41)	0.76 (0.53-1.06)	0.00	
TUMORS OF CENTRAL NERVOUS SYSTEM							
All MHT	483 (0.1)	1.09 (0.99-1.20)	1.07 (0.91-1.24)	1.12 (0.97-1.29)	1.07 (0.86-1.32)	0.10	0.00
Estrogen only MHT	220 (0.1)	1.08 (0.94-1.25)	1.20 (0.91-1.54)	1.11 (0.88-1.38)	0.97 (0.74-1.25)	0.03	
Estrogen plus progestin MHT	263 (0.2)	1.09 (0.96-1.24)	1.01 (0.83-1.22)	1.13 (0.93-1.36)	1.41 (0.92-2.07)	0.00	
KIDNEY CANCER (RENAL CELL)							
All MHT	232	0.92 (0.80-1.04)	1.08 (0.82-1.40)	0.90 (0.72-1.10)	0.83 (0.65-1.05)	0.00	0.11
Estrogen only	126	0.95 (0.79-1.14)	1.21 (0.74-1.87)	0.97 (0.69-1.31)	0.88 (0.66-1.13)	0.01	
Estrogen plus progestin MHT	106	0.87 (0.71-1.06)	1.07 (0.72-1.40)	0.85 (0.63-1.12)	0.67 (0.36-1.14)	0.00	
THYROID CANCER							
All MHT	131 (0.0)	0.93 (0.77-1.11)	0.90 (0.67-1.18)	1.07 (0.78-1.43)	0.80 (0.51-1.19)	0.68	0.15
Estrogen only MHT	72 (0.1)	1.15 (0.89-1.46)	1.41 (0.91-2.08)	1.30 (0.83-1.95)	0.83 (0.50-1.29)	0.29	
Estrogen plus progestin MHT	59 (0.0)	0.75 (0.56-0.98)	0.67 (0.43-0.97)	0.90 (0.56-1.36)	0.71 (0.23-1.66)	0.31	

Supplementary Table 1. The risk of cancer following systemic menopausal hormone therapy (MHT) use by estrogen formulation, progestin type and regimen, and age at first prescription, expressed as standardized incidence ratios (SIR) and 95% confidence intervals (CI).

	Total number of exposed individuals (%)	All Cancers	All gastrointestinal Cancers	Breast Cancer	Ovarian Cancer	Endometrial Cancer	Colon Cancer
Total number of cases in exposed		16,813	2,436	6,376	573	1,211	1,106
Only Estrogen Formulation							
Estradiol	53,339 (39.2)	1.04 (1.00-1.08)	0.89 (0.80-0.99)	1.14 (1.08-1.22)	0.91 (0.72-1.13)	0.23 (0.16-0.31)	0.29 (0.24-0.35)
Estriol	55,653 (40.9)	1.01 (0.98-1.05)	0.89 (0.83-0.96)	0.85 (0.79-0.92)	1.14 (0.93-1.37)	1.92 (1.75-2.11)	0.32 (0.28-0.37)
Tibolone	17,992 (13.2)	1.14 (1.08-1.21)	1.00 (0.85-1.18)	1.36 (1.23-1.49)	0.94 (0.64-1.33)	1.51 (1.23-1.84)	0.38 (0.29-0.50)
Estrogen plus Progestin Therapy							
Progestin Regimen							
Only continuous combinations	92,381 (59.9)	1.18 (1.15-1.21)	0.91 (0.85-0.98)	1.57 (1.51-1.63)	1.06 (0.91-1.22)	0.72 (0.63-0.82)	0.90 (0.81-1.01)
Only sequential combinations	28,263 (18.3)	1.03 (0.96-1.10)	0.86 (0.69-1.05)	1.13 (1.02-1.25)	1.24 (0.88-1.70)	1.14 (0.87-1.47)	0.74 (0.51-1.04)
Progestin Type							
Only Progesterone-derived	47,308 (30.7)	1.14 (1.10-1.19)	0.81 (0.72-0.91)	1.41 (1.33-1.49)	1.23 (1.00-1.50)	1.35 (1.17-1.54)	0.88 (0.74-1.04)
Only Testosterone-derived	85,659 (55.6)	1.19 (1.16-1.22)	0.96 (0.88-1.04)	1.52 (1.46-1.59)	1.20 (1.02-1.39)	0.87 (0.76-0.99)	0.91 (0.80-1.03)
Progestin Regimen and Type							
Progesterone-derived continuous	30,123 (19.5)	1.12 (1.07-1.17)	0.87 (0.75-0.99)	1.49 (1.39-1.60)	1.09 (0.83-1.41)	0.63 (0.48-0.80)	0.86 (0.69-1.06)
Testosterone-derived continuous	53360 (34.6)	1.24 (1.20-1.28)	0.96 (0.87-0.98)	1.70 (1.62-1.78)	1.10 (0.91-1.33)	0.74 (0.63-0.87)	0.93 (0.81-1.07)
Progesterone-derived sequential	3341 (2.2)	1.09 (0.91-1.29)	0.48 (0.21-0.95)	1.25 (0.95-1.60)	1.78 (0.77-3.51)	1.81 (0.99-3.04)	0.73 (0.24-1.70)
Testosterone-derived sequential	21,247 (13.8)	1.05 (0.97-1.13)	0.97 (0.76-1.21)	1.17 (1.04-1.31)	1.24 (0.82-1.79)	0.85 (0.58-1.20)	0.79 (0.51-1.16)

Supplementary Table 2. The association with estimated duration (based on the cumulative dosage per package) of systemic menopausal hormone therapy (MHT) use by MHT types, excluding women exposed in 2005, expressed as standardized incidence ratios (SIR) and 95% confidence intervals (CI).

	Total number of exposed individuals (%)	All Cancers	All gastrointestinal Cancers	Breast Cancer	Ovarian Cancer	Endometrial Cancer	Colon Cancer
Total number of cases in exposed		16,813	2,436	6,376	573	1,211	1,106
Total, years							
<1	58,801 (50.4)	0.97 (0.92-1.02)	0.85 (0.75-0.97)	0.91 (0.84-0.99)	1.12 (0.87-1.43)	1.07 (0.90-1.28)	0.92 (0.77-1.10)
1 to 2	33,013 (28.3)	0.96 (0.90-1.02)	0.85 (0.72-1.00)	1.09 (0.99-1.20)	1.12 (0.81-1.51)	0.59 (0.43-0.80)	0.84 (0.64-1.08)
3 to 4	12,403 (10.6)	0.71 (0.63-0.79)	0.61 (0.43-0.83)	0.73 (0.61-0.87)	0.44 (0.18-0.91)	0.38 (0.19-0.68)	0.59 (0.34-0.95)
More than 5	12,504 (10.7)	0.48 (0.42-0.55)	0.39 (0.27-0.55)	0.37 (0.28-0.48)	0.13 (0.02-0.48)	0.56 (0.33-0.89)	0.38 (0.22-0.61)
Only Estrogen, years							
<1	28,389 (55.5)	1.01 (0.94-1.07)	0.65 (0.53-0.77)	0.92 (0.81-1.03)	1.14 (0.80-1.58)	1.00 (0.78-1.27)	1.00 (0.80-1.24)
1 to 2	11,732 (22.9)	0.91 (0.82-1.00)	0.46 (0.32-0.63)	1.02 (0.87-1.20)	0.87 (0.46-1.48)	0.45 (0.25-0.75)	0.67 (0.43-0.99)
3 to 4	3,308 (6.7)	0.65 (0.53-0.80)	0.26 (0.01-0.58)	0.59 (0.40-0.85)	n=0	0.53 (0.17-1.23)	0.89 (0.41-1.68)
More than 5	7,772 (15.2)	0.50 (0.42-0.59)	0.30 (0.18-0.46)	0.36 (0.24-0.52)	0.24 (0.03-0.85)	0.64 (0.34-1.09)	0.31 (0.15-0.57)
Estrogen plus progestin, years							
<1	30,412 (46.4)	0.92 (0.86-0.99)	0.94 (0.77-1.13)	0.91 (0.80-1.02)	1.07 (0.72-1.53)	1.17 (0.89-1.50)	0.78 (0.55-1.07)
1 to 2	21,281 (32.5)	1.01 (0.93-1.09)	0.80 (0.62-1.00)	1.14 (1.01-1.29)	0.81 (0.48-1.27)	0.71 (0.48-1.02)	1.01 (0.71-1.39)
3 to 4	9,095 (13.9)	0.73 (0.64-0.84)	0.41 (0.24-0.66)	0.78 (0.64-0.96)	0.54 (0.20-1.18)	0.31 (0.11-0.67)	0.41 (0.16-0.84)
More than 5	4,732 (7.2)	0.45 (0.36-0.56)	0.32 (0.14-0.64)	0.38 (0.25-0.55)	0.15 (0.00-0.85)	0.43 (0.14-1.01)	0.10 (0.00-0.54)

Appendix 1. Cancer categorization by anatomical location using International Classification of Disease 10th edition (ICD-10).

	ICD-10
Breast and gynecological cancers	
Breast	C500-6, 8-9
Endometrium	C540-1, 3, 9; C559
Ovaries	C56; C570-4, 7-9
Cancers of the gastrointestinal tract	
Esophagus and cardia	C150-5, 8-9, C160
Gastric	C161-6, 8-9
Pancreas	C250-4, 7-9
Gallbladder and bile ducts	C239; C240-1, 8-9
Liver	C220-1, 9
Colon	C180-9; C260,
Rectum	C199; C209; C21-2
Other cancers	
Lung	C339; C340-3, 8-9, C384, C398
Malignant melanoma	C430-9
Central nervous system	C700-1, 9; C710-9; C720-5, 8-9; C752-3
Bladder	C670-9
Kidney	C64
Thyroid	C739

Appendix 2. Sensitivity analysis by excluding the first calendar period (2005-2006) for those cancers with the strongest associations by MHT types, expressed as standardized incidence ratios (SIR) and 95% confidence intervals (CI).

	SIR (95% CI)	
	Years 2005-2012	Years 2007-2012
All incident cancers		
All MHT	1.09 (1.07-1.11)	1.12 (1.10-1.14)
Estrogen MHT	1.04 (1.01-1.06)	1.07 (1.04-1.10)
Estrogen plus progestin MHT	1.14 (1.12-1.17)	1.16 (1.14-1.19)
All gastrointestinal cancers		
All MHT	0.90 (0.86-0.94)	0.93 (0.89-0.97)
Estrogen MHT	0.91 (0.86-0.96)	0.95 (0.90-1.01)
Estrogen plus progestin MHT	0.88 (0.83-0.94)	0.91 (0.85-0.97)
Breast cancer		
All MHT	1.24 (1.21-1.27)	1.26 (1.22-1.29)
Estrogen MHT	1.05 (1.01-1.10)	1.08 (1.03-1.13)
Estrogen plus progestin MHT	1.40 (1.36-1.45)	1.40 (1.36-1.45)
Endometrial cancer		
All MHT	1.12 (1.06-1.19)	1.15 (1.07-1.22)
Estrogen MHT	1.17 (1.08-1.27)	1.19 (1.09-1.30)
Estrogen plus progestin MHT	1.07 (0.98-1.17)	1.10 (1.00-1.21)
Ovarian cancer		
All MHT	1.09 (1.00-1.19)	1.12 (1.02-1.23)
Estrogen MHT	1.03 (0.91-1.17)	1.02 (0.88-1.17)
Estrogen plus progestin MHT	1.15 (1.03-1.29)	1.22 (1.08-1.37)
Colon cancer		
MHT	0.90 (0.84-0.95)	0.92 (0.86-0.98)
Estrogen MHT	0.91 (0.84-0.99)	0.95 (0.86-1.02)
Estrogen plus progestin MHT	0.88 (0.80-0.97)	0.91 (0.82-1.00)